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(54) Encapsulated medicament in sweet matrix

(57) An orally administrable medicament is prepared into a dosage form which eliminates the unpleasant taste and mouth feel of the medicament and is easily and pleasantly ingested even by children, by microencapsulating the medicament and embedding the microcapsules into a soft, sweet palatable matrix, such as chocolate.

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SPECIFICATION

Microencapsulated medicament in sweet matrix

Field of the Invention

The present invention relates to a manner in which medicaments may be orally administered to children or others in a pleasant manner in which the taste of the medicament is totally hidden. More particularly, the present invention relates to a medicament form for permitting such administration.

Background of the Invention

Oral medication is one of the most popular methods of drug administration into the body because it enables self-medication of the patient. In this category, palatability is an extremely important factor in formulating pharmaceutical forms. Because of the strong upleasant taste of many medicaments the value of many drugs is substantially diminished. This is particularly common among children's medications, but is also true for adults. In order to overcome these problems of unpleasant taste and unpalatable taste, many flavorings have been employed with pharmaceuticals. Thus, it is very common to administer many children's drugs as flavored syrup. Unfortunately, flavoring merely masks the unpleasant mouth taste but affects the palatability only slightly. A number of medications have an especially bitter taste, and even adults reluctantly take them. In many such cases even syrups cannot mask the bitter taste, thus constituting a difficult pharamaceutical problem.

Among the flavorings which have been used for the purpose of masking is chocolate. Examples of patents in which chocolate is used in conjunction with medicaments, are U.S. patents 4,271,142 and 4,327,077 to Puglia et al, U.S. patent 3,697,641 to Ahrens, U.S. patent 199,139 to Clark, British patent 543,309 to Evans and Australian patent 7310/32 to Jones et al. Children's vitamins encased in chocolate are also known and on the market, but in these products same of the vitamins are not sufficiently stable. Laxatives in chocolate are also well known. In all of these, however, the unpleasant taste is merely masked and the medicines still adversely affect the flavor of the chocolate and the palatability of the medicine is not substantially improved. Furthermore, stability problems caused by direct contact of the drug with the chocolate can arise.

In order to permit the release of orally administered drugs within selected portions of the alimentary canal, i.e. the stomach or intestine, pills in which the medicaments are protected with the desired coating have been developed. A more advanced pharmaceutical form for this purpose is the microencapsulated drug where one tablet (or large capsule) contains a few hundred tiny (approximately 0.5–0.8mm) capsules (called microcapsules) constaining the drug. The type of coating encapsulating the drug is chosen according to the medication desired and the desired release characteristics.

Summary of the Invention

It is an object of the present invention to provide a new form of medication for oral administration.

It is another object of the present invention to provide a new form of medicament for oral administration in which the unpalatable taste and mouth feel of the medicament is totally eliminated.

It is further object of the present invention to provide a new form of medicament which is very palatable to children, as well as to adults.

It is yet another object of the present invention to provide a method for administering medicaments for children in a manner which will be palatable to the child.

These and other objects are obtained in accordance with the present invention by micoencapsulating the drug to be administered and embedding the microcapsules in a soft sweet palatable matrix such as chocolate. The combination of encapsulation of the drug and the use of the soft sweet matrix, such as chocolate, achieves the goals of both preventing the unpleasant taste which the drugs may possess and overcoming the palatability problem that may arise when one tries to ingest the drug itself. The encapsulation will prevent the unpleasant taste which many drugs possess and the chocolate matrix will serve as a way to overcome the palatibility problem. Furthermore, the encapsulation will avoid the medication giving an off-flavor to the chocolate itself, which inevitably occurs when drugs are mixed directly with a chocolate matrix without first being microencapsulated and will avoid loss of stability of the medicament by eliminating direct contact of the medicament with the chocolate.

This combination will totally eliminate the unpleasant taste of the medicines and the patient will only taste the chocolate or other soft sweet matrix. Obviously, this system is superior to any other existing method.

Detailed Description of Preferred Embodiments

As the soft sweet matrix in accordance with the present invention, there may be used any palatable foodstuff which can be masticated without substantial chewing and easily swallowed, preferably a confection which is sweet to the taste and will be readily accepted by the child or adult. While chocolate is the preferred matrix, it should be understood that other soft sweet matrices such as fudge, marshmallows, peanut butter, carob, solid yogurt, or even cookies of appropriate consistency may be used as the matrix, alone or in combination with other matrices. The matrix cannot be hard, such as a hard candy, because the heavy pressure which would be involved in chewing such a matrix would break the microcapsules and thus destroy the purpose of the present invention. A soft chocolate, such as sweet or milk chocolate, is ideal for this purpose as substantial chewing is not required for complete mastication and the chocolate and embedded microcapsules can be masticated and swallowed without breaking the microcapsules.

The microcapsules should be of small size in order to ensure easy and pleasant palatability. Thus, the size should be less than 2mm diameter, preferably less than 1mm in diameter, and most preferably in the range of 10–100 microns. The smaller the microcapsules, the less likely they are to be noticed by the patient, and the more likely that the capsules will escape chewing and essentially will be swallowed intact.

A very wide range of medicaments are suitable for inclusion in the microcapsules used in the present invention. Such medicaments include antibiotics and other antibacterial agents, analgesics, antihistamines, decongestants, anti-inflammatory agents anti-hypertensive agents, hypnotics, sedatives, tranquilizers, alkaloids, diuretics, vasodilators, hormones, vitamins or any other medicament frequently used in oral dosage form. Those with especially bitter taste, such as penicillin, are, of course, particularly suited for use in the present invention.

Suitable antibiotics include penicillins, cephalosporins, tetracyclines, chloramphenicol, streptomycins, and macrolids. Suitably fully synthetic anti-bacterial agents include nitrofurantoin and the sulphonimides. Suitable anti-inflammatory or analgesic agents include aspirin and acetaminophen. Suitable pyschotropic medicaments include -methyldopa and guanethidine. Suitable diuretics include aminophyline and acetazolamide.

Antibacterials include benzylpenicillin, phenoxymethylpenicillin, ampicillin and its pivaloyloxymethyl or phthalyl esters, amoxycillin, cloxicillin, dicloxicillin, flucloxicillin, carbenicillin, propicillin, methicillin, cephalexin, cephaloridine, cephaloglycine, cephalothin, tetracycline, oxytetracycline, chlorotetracycline, novobiocin, neomycin, chloramphenicol, sulphathiazole, succinyl sulphathiazole, sulphadimidine, streptamycin, erythromycin, fusidic acid, griseofulvin, kanamycin, lincomycin, spiramycin, sulphamethoxy pyrideazine, sulphaphenazole, salicylazosulphapyridine, sulphamethoxazole and trimethoprin.

Suitable vitamins or nutritional supplements include thiamine, nicotinamide, ascorbic acid, pyridoxine, riboflavine, tryptophan, pantothenates, glycerophosphates and mixtures of these and other vitamins.

Other medicaments include alcofenac, theophylline, hexobendine, xylamide, and 0-(4-methoxyphenylcarbomoyl)-3-diethylaminopropiophenone oxime.

Normally any of the medicaments to be microencapsulated may be used as their conventional salts, hydrates or the like.

This list is not intended to be all inclusive as any medicament which can be microencapsulated may be administered in the form of the present invention.

A broad range of encapsulating agents and methods of encapsulation may also be used in the present invention. The only limitations on the encapsulation material are that it must be such that the active core material will not come into contact with the chocolate, or other matrix, during production or storage, it must be non-toxic and harmless, it must allow the core material to become released in the stomach or gastro-intestinal tract and it must be compatible with the sweet matrix. Any capsule materal known to the art may be used in the present invention and any method of microencapsulation may be used. See, for example, the methods of microencapsulation discussed in Sparks, R.E., "Microencapsulation", *Kirk-Othmer Encyclopedia of Chemical Technology*, third edition, volume 15 (1981), pages 470–493. As is well known, the microencapsulation material may be chosen for sustained release properties or for release in a preferred area of the alimentary canal (e.g., stomach or intestine). It is preferred that a method be used such that as high a weight percent as possible of the microcapsules be active material. For example, U.S. patent 4,016,254 teaches a method of microencapsulation in which the microcapsules have an average diameter of from 100μ to 300μ and which comprise 94% to 99.9% of a medicament coated by 0.1% to 6% of a coating agent. See also U.S. patent 3,119,742. Any such microencapsulation procedure known to the art or discovered by the art in the future may be used to make the encapsulated medicament for use in the present invention. The present invention does not relate to techniques of microencapsulation per se, but only to the use of microcapsules of medicaments in a soft sweet matrix such as chocolate.

The amount of microcapsules to be loaded into a single dosage unit will depend upon the [illegible] being administered. For example, 200mg can

easily be formed into microcapsules and dispersed in a bite size unit dosage of matrix in a manner which will be substantially undiscernible to those eating the matrix. The maximum loading of microcapsules into the matrix will to a large extent be dependent upon the size of the microcapsules, the smaller the microcapsules, the larger the amount that can be loaded without being noticed when the matrix is ingested. For very tiny microcapsules, for example on the order of the size used in carbonless copy papers, it is conceivable that amounts as high as 50%, or even more, could be used without adversely affecting the consistency of the matrix. For example, if the dosage morsel of chocolate is very small, a unit dosage of medicament in very small microcapsules may be 500 mg in 1 gram of chocolate. Such a heavy loading, however, would not be preferred as substantial breakage of the microcapsules during chewing would be nearly unavoidable. However, the loading preferably should not exceed about 25–30% of the weight of the matrix and is most preferably less than 10%, depending on the average dose of the particular medicament being administered and the desired size of the dosage unit of matrix. A substantially bite-size dosage of matrix will generally be about 1–15g, depending on the density of the matrix.

When the matrix is chocolate, the microcapsules are preferably added to the chocolate in the process of its original production. For example, sweet chocolate and milk chocolate are made by mixing cocoa butter, sugar, chocolate liquor and, for milk chocolate, milk or milk solids. These are then refined to a fine particle size and then subjected to conching. Conching is a kneading process in which chocolate is slowly mixed, allowing moisture and volatile acids to escape while smoothing the remaining chocolate paste. Conching temperatures for sweet chocolate generally range from 55–85°C and from 45–55°C for milk chocolate. It is conventional to add flavors, emulsifiers, etc. during conching. Thus, the most appropriate time to add the microcapsules of the present invention in the chocolate production is also during conching. Of course, care must be taken that sufficient mixing occurs to obtain a substantially homogeneous distribution of microcapsules so that an accurate amount of medicament will be present in any given unit weight of chocolate.

Following conching, the product is standardized, tempered and molded in well known manners.

The microcapsules need not be added during conching, but may be added at any appropriate step during the production of chocolate, or may be added by taking completed chocolate, melting it, adding the microcapsules, mixing to homogeneity, and then again molding.

It should be understood that the manner of adding the microcapsules to the chocolate or other soft sweet matrix is not critical and any procedure can be used so long as a substantially homogeneous distributon of microcapsules is obtained.

Example 1

The microcapsules used in this example are those of the commerical drug "Contac", manufactured by Menley and James Laboratory (a Smith Kline Company). Each capsule contains 600 microcapsules, each of a diameter of about 0.5–0.8 mm. The microcapsules are prepared by pan-coating. Each capsule (i.e. 600 microcapsules) contains 75 mg phenylpropanolamine hydrochloride and 8 mg chlorpheniramine maleate.

The 600 microcapsules of one Contac capsule were embedded into chocolare by first heating a commercial chocolate square to melting (50°C) in an aluminum pan container, and then adding and mixing the microcapsules until a homogenous distribution of the capsules in the chocolate matrix was achieved, approximately 3 minutes. The chocolate was immediately cooled and molded into a unit of approximately 32mm × 20mm × 9mm.

When this chocolate was chewed, no taste of the drug was observed compared to a strong taste which was observed when the capsules were chewed without the chocolate. In addition, there was essentially no granular sensation upon chewing the chocolate pieces.

A sample of this chocolate was stored over one month at room temperature and then observed visually, and the stability of the drug was analyzed by mass spectroscopy analysis. After one month there was no change in the shape or number of the embedded microcapsules, and 100% of them could be recovered from the chocolate matrix. Mass spectrometic analysis of the embedded encapsulated drug showed it to be identical to a control sample (i.e., original microcapsules stored in commercial package). Thus, the introduction of the microcapsules into the chocolate matrix did not affect the stability or the chemical or physical state of the drugs in the microcapsules.

Example 2

The microcapsules used in this example were those of the commercial drug "Sudafed, S.A.", manufactured by Burroughs Wellcome Co. Each capsule contains about 300 microcapsules (diameter 0.6–0.9 mm). Each large capsule contains 120mg pseudoephedrine hydrochloride. These microcapsules were embedded in a single regular chocolate unit in the manner described in example 1. When the chocolate tablet was chewed and swallowed, no unpleasant taste of the

drug was detected.

Example 3

Microcapsules of aspirin coated with a hydrolized protein (gelatin) with an average diameter of 1.7μ to 2.0μ, each microcapsule comprising 99% aspirin, are prepared in the manner set forth in example 59 of U.S. patent 4,016,254. 40.4g of such microcapsules are added to 1kg of milk chocolate during the conching stage of the production thereof. After mixing to homogeneity, chocolate is standardized and tempered in a conventional manner, and then poured into molds to produce units of approximately 5g each. Each unit contains microcapsules which include 200mg of aspirin. The chocolate units may be chewed and swallowed with no unpleasant taste of aspirin being detectable.

Example 4

Microcapsules of aspirin coated with hydroxyphenylmethyl cellulose are prepared using the all-metal, conical Uni-Glatt 4"-Wurster apparatus. The average size of aspirin microcapsules was 80–180μ, in with each microcapsule comprising 93% aspirin and 7% coating.

A similar coating, under the same conditions, was carried out using cellulose acetylphthalate as coating material.

The above prepared microcapsules were embedded in chocolate (100mg encapsulated material per 1.5g chocolate) in the manner described in example 1. When the chocolate tablet was chewed and swallowed, no unpleasant taste of the drug was detected.

Example 5

Acetaminophen was encapsulated in 2.4% ethyl cellulose (Ethocel) and 1.05 hydroxypropylmethylcelluloe phthalate (HP 50). This coating was performed on the Aeromatic Strea-l fluidized bed apparatus. The average size of the obtained microcapsules was 80–120μ. The microcapsules were embedded in chocolate (100mg encapsulated material per 1.5g chocolate) in the matter described in Example 1. When the chocolate tablet was chewed and swallowed, no unpleasant taste of the drug was detected.

Example 6–13

The following drugs, each in encapsulated form with diameter of about 500–600μ, were embedded in 1.5g chocolate in the unit dosages specified. In each case no unpleasant taste of the drug was detected upon chewing and swallowing of the chocolate formulation.

Example No.	*Active Principle*	*Unit Dosage*
6	Theophylline	200 mg
7	Chlorpromazine hydrocloride	75 mg
8	Chlorpheniramine maleate	8 mg
9	Erythromycin	250 mg
10	Ferrous sulphate heptahydrate	167 mg
11	Nitroglycerin	2.5 mg
12	Papverine hydrochloride	150 mg
13	Niacin	250 mg

It will be obvious to those skilled in the art that various changes may be made without departing from the scope of the invention and the invention is not to be considered limited to what is described in the specification.

CLAIMS

1. A dosage form for the oral administration of a pharmaceutical active principle, comprising:

microencapsulated active principle embedded in a soft sweet palatable matrix.

2. A dosage form in accordance with claim 1, wherein a sufficient quantity of microencapsulated active principle is present in said matrix to provide a unit dose of said active principle in each bite-size unit of said matrix.

3. A dosage form in accordance with claim 1, wherein said soft, sweet, palatable matrix is sufficiently soft as to allow mastication thereof without the necessity of substantial chewing.

4. A dosage form in accordance with claim 1, wherein said matrix is selected from the group consisting of chocolate, fudge, marshmallow, peanut butter, carob or solid yogurt.

5. A dosage form in accordance with claim 1, wherein said matrix is chocolate.

6. A dosage form in accordance with claim 1, wherein said matrix is sweet chocolate or milk chocolate.

... claim 1, wherein said active principle is an anti-

sive agent, hypnotic, sedative, tranquilizer, alkaloid, diuretic, vasodilator, hormone or vitamin.

8. A dosage form in accordance with claim 1, wherein said microcapsules of active principle have a diameter of less than 1 mm.

9. A dosage form in accordance with claim 1, wherein said microcapsules of active principle have a diameter of about 10–100 microns.

10. A dosage form in accordance with claim 1, wherein the active principle is encapsulated in a material which prevents the active principle from coming into contact with said matrix throughout production and storage of the embedded matrix prior to use, is non-toxic and harmless, and permits release of the active principle in the stomach or gastro-intestinal tract after ingestion.

11. A method for oral administration of a pharmaceutical active principle without unpleasant or unpalatable taste or mouth feel, comprising:

orally administering to the patient a unit dose of a dosage form in accordance with claim 1.

12. A method in accordance with claim 11, wherein the patient is a child.

13. A method for the production of a dosage form for the oral administration of a pharmaceutical active principle, comprising:

microencapsulating the active principle; and

embedding the microencapsulated active principle in a soft, sweet, palatable matrix.

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